REMARKS

In view of the remarks put forth below, reconsideration and allowance of the pending claims is respectfully requested.

FORMAL MATTERS

Claims 1-4, 6, 8-11, 15, as well as, new Claims 19-30 are pending after entry of the amendments above.

New Claims 19-30 are added. Support for these claims is found in the claims as originally filed as well as in the Specification at, for example, page 11, paragraphs 46-47, page 20, paragraph [0087] (lines 8-9), page 25, paragraph [0108] (line 1), original Claims 6 and 8.

Claims 5, 7, 12-14, and 16-18 have been cancelled without prejudice.

No new matter is added.

REJECTION UNDER 35 U.S.C. §103(A)

Claims 1-4, 6, 8-11, and 15-18 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Stiefel et al. (U.S. Patent No. 6,656,509) in view of Lemelson (U.S. Patent No. 4,665,897) and Gorun (U.S. Patent No. 6,511,971). This rejection is respectfully traversed.

In addition to demonstrating that all elements were known in the prior art, the Office must provide evidence that the combination would be "a predicted success." This principle is illustrated in *three* Supreme Court cases[1] decided prior to *KSR*, and is a recurring theme of *KSR*. For example, in *KSR*, the Supreme Court stated that in order for a combination of elements to be patentable, "the combination must do more than yield a predictable result".[2] Likewise, the corollary principle, namely that "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results"[3] is also discussed. The Supreme Court in *KSR* also stated that "a court *must* ask whether the

[1] *United States* v. *Adams*, 383 U.S. 39, 40 (1966); *Anderson's-Black Rock, Inc.* v. *Pavement Salvage Co.*, 396 U.C. 57, 60-62 (1969); and *Sakraida* v. *AG Pro, Inc.*, 425 U.C. 273, 282 (1976).
[2] *KSR International v. Teleflex Inc.*, 127 S. Ct. 1727, 1740 (2007).
[3] *KSR International v. Teleflex Inc.*, 127 S. Ct. 1727, 1739 (2007).

improvement is more than the predictable use of prior art elements according to their established functions".[4]

In making this rejection, the Examiner states the following:

> The difference between Stiefel et al. and the claimed invention is that Stiefel et al. does not expressly disclose the use of inorganic selenite, radiation therapy or reactive oxygen species (ROS)-inducing therapy. However, the prior art amply suggests the same as Steifel et disclose that sodium selenite is a preferred source of selenium, the applicant acknowledges that radiotherapy is used to treat prostate cancer, Lemelson discloses use of radiation therapy using neutron beams to active nuclides species at the site of the tumor and Gorun discloses that photodynamic sensitizers which produce singlet molecular oxygen are used to destroy cancerous tissue. As such, one of ordinary skill in the art would have expected that the combination of sodium selenite with other methods of treatment of cancers and tumors would be effective in treating cancers and tumors such as prostate cancer.

(Office Action dated July 7, 2009, page 3)

The Examiner further states:

> The Applicant argues that evidence of synergistic activity has been provided. Said evidence consists of specific amounts of and types of selenite and radiation against two cell lines in vitro and a conclusion that treatment of mice with single cell line tumors, without presenting any data, that that the effect was significantly greater than that of radiation or selenite alone.
>
> With respect to the mice, no data is provided, as such, the Examiner is unable to determine whether or not the Applicant's conclusions are valid with respect to any synergistic activity.

(Office Action dated July 7, 2009, page 4)

The Applicants submit that the combination of the references does not render the claimed invention obvious because the combination of the cited references fail to provide one of skill in

[4] *KSR International v. Teleflex Inc.*, 127 S. Ct. 1727, 1740 (2007); emphasis added.

the art with predicted success in the claimed methods and because the claimed invention yields unexpectedly improved properties not present in the prior art. Arguments in support of the Applicants' assertion have been provided in the amendment submitted on April 14, 2009 and are not reiterated here for sake of brevity.

With regards to the Examiner's assertion that the conclusion presented in example 10 of the specification that the effect of the combined treatment (with selenite and radiation) was significantly greater than that of radiation or selenite alone is not accompanied by data and hence the Examiner cannot determine the validity of the Applicants' conclusion, the Applicants submit that all statements in the specification are presumed to be true unless the Examiner can establish to the contrary. The Applicants remind the Examiner that the Applicants submitted a declaration under 37 CFR §1.63 with the instant patent application that states

> **All statements made herein of my/our own knowledge are true, all statements made herein on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and may jeopardize the validity of the application or any patent issuing thereon.**

Thus, in view of the Applicants' declaration that "all statements made herein of my/our own knowledge are true, all statements made herein on information and belief are believed to be true", the Examiner should accept the statement in the specification to be true unless proven otherwise, and ascribe the proper weight to the statement presented in example 10 for determining obviousness of the claimed invention under § 103(a).

Nevertheless, the Applicants provide herewith evidence in the form of a Declaration under 37 C.F.R. §1.132 by one of the inventors, Dr. Susan Knox. In summary, the declaration states:

1. Well established mouse models for prostate cancer were used to study the radiosensitizing effect of sodium selenite (SSE) in prostate cancer cells. A murine model was also used to study the radiosensitizing effect of SSE on normal radiosensitive intestinal crypt cells. Immunodeficient (SCID) mice with hormone-independent LAPC-4 (HI-LAPC-4) and PC-3 xenograft tumors (~200mm3) were divided in 4 groups: control (untreated), XRT (local irradiation), SSE (2 mg/kg, IP, TIW), and XRT+SSE. The radiosensitizing effect

of SSE on normal intestinal epithelial cell was assessed using a crypt cell microcolony assay.

2. SSE alone significantly inhibited the tumor growth in LAPC-4, but not PC-3 tumors. SSE significantly enhanced the XRT-induced tumor growth inhibition in both LAPC-4 and PC-3 tumors. (See Fig. 1).

3. SSE did not affect the intestinal crypt cell survival either alone or in combination with XRT. (See Figs. 2 and 3).

4. Thus, SSE significantly enhances the effect of radiation on well-established hormone-independent prostate tumors, and does not sensitize the intestinal epithelial cells to radiation. This is important since intestinal epithelium is clinically relevant to the treatment of prostate cancer with irradiation. If SSE radiosensitized normal intestinal epithelial cells, the gain in therapeutic index from using this therapeutic approach would have been jeopardized.

5. The growth of HI-LAPC-4, but not PC-3 xenograft tumor, was inhibited by SSE treatment alone, possibly due to the lack of wild type androgen receptor (AR) in PC-3 cells. We have previously found that SSE inhibits AR expression and function in LAPC-4 cells, whereas the wild type AR expression is maintained in HI-LAPC-4 cells. Given the importance of AR in prostate cancer cell growth, the inhibitory effect of SSE alone would be expected to be limited in PC-3 cell lines. However, the observation that SSE enhanced the response of both tumor types to radiation suggests that the radiosensitizing effect of SSE is independent of AR status. Since, radiosensitizing effect of SSE is independent of AR status, SSE is likely to radiosentitize other types of tumors, in addition to prostate cancer.

6. Thus, it is reasonable to extrapolate the results obtained from prostate cancer mouse models to other types of cancer and to conclude that the combination of a salt of an inorganic selenium-containing compound and radiation therapy may be used to treat neoplastic disease, to enhance sensitivity

of a tumor, and to treat prostate cancer, independent of the type of tumor or the particular salt of inorganic selenium (i.e., salt of selenite or selenate).

7. The results of the experiment described in Example 10 refer to data obtained from a pilot experiment that was performed prior to filing of the application that first contained Example 10. This observation has been further confirmed by later work, such as that described above.

MPEP §716.02(e) states that "A greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness ...of the claims at issue." The cited reference Stiefel discloses a selenium compound, but not radiation therapy, as recited in the present claims. The cited reference Lemelson discloses radiation therapy, but not a pharmaceutically acceptable salt of an inorganic selenium-containing compound. The cited reference Gorun discloses a photosensitizing compound, but not a pharmaceutically acceptable salt of an inorganic selenium-containing compound.

Applicants submit that one of ordinary skill in the art, even in view of Siefel, Lemelson, and Gorun would not reasonably expect that a combination of a pharmaceutically acceptable salt of an inorganic selenium-containing compound and radiation therapy would provide for synergistic inhibition of the growth of cancer cells. Indeed, the results from Examples 5, 6, and 10, as well as, those provided in with the § 1.132 Declaration show significant beneficial effect for a combination of a pharmaceutically acceptable salt of an inorganic selenium-containing compound and radiation therapy that would not have been predicted by one of ordinary skill in the art.

In light of the above arguments, it is submitted that the cited combination of references fails to provide the requisite predicted success in the claimed methods. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. §103(a).

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone Carol Francis at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-333.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

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Enclosure(s): Declaration under 37C.F.R. §1.132
Figs. 1-3

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